CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-488

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND RHEUMATOLOGY PRODUCTS

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of Drug Evaluation II
Division of Anesthesia, Analgesia and Rheumatology Products

NDA:	NDA 022488
PRODUCT:	Lyrica (pregabalin) oral solution, 20 mg/mL
SPONSOR:	C.P Pharmaceutical International C.V. c/o Pfizer, Inc.
FROM:	Robert Shibuya, M.D. Clinical Team Leader
THROUGH:	Rigoberto Roca, M.D. Deputy Director, DAARP
DATE:	January 4, 2010

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug
(F) Whether the drug is a new molecular entity.

In this NDA 22-488, the sponsor proposes a new formulation of LYRICA® (pregabalin), oral solution 20 mg/mL. The initial approved oral capsule formulation of LYRICA® (NDA 21-446) has a REMS that was approved on April 23, 2009.

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for LYRICA® (pregabalin) oral solution to ensure that the benefits of the drug outweigh the risks of suicidal thoughts and behavior with the class of antiepileptic drugs, of which LYRICA® (pregabalin) oral solution is a member. In reaching this determination, we considered the following:

A. It is not possible to precisely estimate the size of the population likely to use LYRICA® (pregabalin). However it is anticipated to be large, based on the use of antiepileptic drugs in general. Many antiepileptic drugs are also approved for the treatment of other illnesses including bipolar disorder, trigeminal neuralgia, migraine, postherpetic neuralgia, pain from diabetic peripheral neuropathy, and fibromyalgia (Attachment 1). The age-adjusted prevalence of epilepsy in developed countries is 4 to 8 per 1,000. It is estimated that approximately three million people in the United States have epilepsy. The total number of patients receiving a prescription for any of the 11 antiepileptic drugs included in the meta-analysis of the risk for suicidal thoughts and behavior with antiepileptic drugs (described below in Section E) in outpatient retail pharmacies in the United States was over 11 million in 2007 (Attachment 2). Usage has increased over time.

B. Patients with epilepsy have approximately two to three times the risk of death from any cause compared with persons without epilepsy. Many of the deaths in persons with epilepsy are directly related to seizures, accidents and injuries arising from seizures, and the underlying condition resulting in seizures. Antiepileptic drugs are also approved for a variety of other treatment indications (Attachment 1). Many of these illnesses are also associated with substantial morbidity and an increased risk of mortality.

C. Antiepileptic drugs have a demonstrated ability to reduce frequency of seizures when used for treatment of epilepsy. Since many deaths in persons with epilepsy are directly related to seizures, antiepileptic drugs reduce mortality in this population of patients. Some antiepileptic drugs also are approved for the treatment of conditions other than epilepsy (Attachment 1).

D. Antiepileptic drugs are used as chronic therapy in patients with epilepsy. Duration of treatment may vary for other treatment indications.

E. A known serious risk of antiepileptic drugs as a therapeutic class is an increased risk of suicidal thoughts and behavior (which are risk factors for completed suicide). The increased risk of suicidal thoughts and behavior were demonstrated in a meta-analysis of randomized, parallel-arm, placebo-controlled clinical trial data for 11 AEDs. [1]

---

[1]Statistical review and evaluation: Antiepileptic drugs and suicidality. (Accessed September 24, 2008, at http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4372b1-01-FDA.pdf.)

In the meta-analysis, the odds ratio for suicidal behavior or ideation for all AEDs studied was 1.80 (95% CI: 1.24, 2.66); 0.37% of all drug-treated patients and 0.24% of placebo-treated patients had an event of suicidal behavior or ideation. This finding was generally consistent among drugs in the data analyzed. It was shared by drugs with varying mechanisms of action and was observed for all indications studied; this observation suggests that the risk applies to all antiepileptic drugs regardless of indication of use.

The background incidence of suicide in patients with epilepsy is estimated as being higher than the incidence of suicide in the general population. Estimates of the incidence of suicide in patients with epilepsy vary widely, but studies have consistently indicated a higher incidence of suicide (and suicide attempts) in patients with epilepsy. The background incidence of suicide is also estimated as being higher in other conditions for which antiepileptic drugs are indicated, including bipolar disorder. In patients with bipolar disorder, the estimated rate of suicide is 0.40% per year (compared to the international general population average of 0.017% per year); the standardized mortality ratio is estimated to be 22.

In addition to the above referenced data and meta-analysis indicating an increased risk for suicidal thoughts and behavior, LYRICA® (pregabalin) has been associated with various other adverse effects including angioedema, hypersensitivity reactions, peripheral edema, dizziness and somnolence, and a known potential to increase seizure frequency upon rapid discontinuation of LYRICA® (pregabalin).

F. LYRICA® (pregabalin) is not a new molecular entity.

In accordance with section 505-1 of the FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for LYRICA® (pregabalin). FDA has determined that LYRICA® (pregabalin) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of LYRICA® (pregabalin). FDA has determined that LYRICA® (pregabalin) is a product for which patient labeling could help prevent serious adverse effects and that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decisions to use, or continue to use LYRICA® (pregabalin).

The elements of the REMS for LYRICA® (pregabalin) will be a Medication Guide and a timetable for submission of assessments of the REMS.

Attachment 1

FDA-approved non-epilepsy treatment indications of antiepileptic drugs (AEDs) with data in the FDA analysis of AEDs and suicidality

Drug	Treatment Indications
Carbamazepine	trigeminal neuralgia
Gabapentin	Postherpetic neuralgia
Lamotrigine	bipolar disorder (maintenance)
Pregabalin	neuropathic pain from diabetic peripheral neuropathy, postherpetic neuralgia, fibromyalgia
Topiramate	Migraine
Divalproex sodium	mania, migraine

Attachment 2

Total number of unique patients receiving a prescription for any of 11* antiepileptic drugs in U.S. outpatient retail pharmacies, 2002-2007

year	2002	2003	2004	2005	2006	2007
# patients	(b) (4)					

*11 drugs included: carbamazepine, divalproex sodium, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, and zonisamide.

Source: Verispan, Vector One Total Patient Tracker

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22488	ORIG-1	PFIZER CHEMICAL CORP	LYRICA (PREGABALIN)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT B SHIBUYA
01/04/2010

RIGOBERTO A ROCA
01/04/2010

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	December 14, 2009
To:	Bob Rappaport, MD, Director Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)
Through:	Claudia Karwoski, PharmD, Director Division of Risk Management (DRISK)
From:	Mary Dempsey, BS, Coordinator Risk Management Programs, DRISK LaShawn Griffiths, MSHS-PH, BSN, RN Acting Team Leader, Patient Labeling Reviewer, DRISK
Subject:	Review New Supplement for (NDA 21-446) Lyrica (pregabalin) including REMS Modification and REMS Assessment and Proposed Risk Evaluation and Mitigation Strategy (REMS) for (NDA 22-448) Lyrica Oral Solution
Drug Name(s):	Lyrica (pregablin) Capsules and Oral Solution
Application Type/Number:	NDA: 021446 NDA: 022448
Applicant/sponsor:	Pfizer Global Research and Development
OSE RCM #:	2009-1082

1. Background

The Lyrica Capsules (NDA 21-446) Risk Evaluation and Mitigation Strategy (REMS) was approved April 23, 2009. The REMS includes a Medication Guide (MG) and a Timetable for Submission of Assessments. Lyrica Oral Solution (NDA 22-488) was submitted for approval March 4, 2009. On June 8, 2009 DRISK received a request from the Division of Anesthesia, Analgesia and Rheumatology Products (DAARP) to review the Lyrica Oral Solution MG and subsequently to review the REMS Modification and proposed REMS submitted November 30, 2009. The proposed REMS modification applies to all Lyrica NDAs.

2. Material Reviewed

- April 23, 2009 Lyrica Capsules REMS approval including Medication Guide
- November 30, 2009 Lyrica Capsules Prior Approval REMS Modification Supplement
- November 30, 2009 submission to Lyrica NDAs containing proposed REMS Modification including Medication Guide and REMS Assessment

3. Proposed REMS Elements

The cover letter of the Lyrica Oral Solution November 30, 2009 submission which provides cross-reference to Lyrica Capsules Prior Approval Supplement contains the proposed REMS Modification, REMS Assessment and proposed REMS with Medication Guide and states the following:

> "The only changes made to the approved REMS and Medication Guide include additional reference to the Lyrica oral solution; no safety information was added or revised, and the timetable for assessment remains unchanged.
>
> A REMS assessment is not included as part of this submission because insufficient time has passed since approval of the REMS to provide a meaningful assessment."

4. Conclusion and Recommendation

DRISK performed an electronic comparison of the November 30, 2009 submitted REMS and Medication Guide to the approved REMS and Medication Guide and found the documents to be identical with the exception of the addition of Lyrica Oral Solution text; no safety information was added or revised.

DRISK agrees that the Sponsor's proposed REMS Modification for Lyrica products meets the statutory requirements in accordance with section 505-1 of FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. The proposed REMS modification is acceptable for all Lyrica NDAs. We have made some editorial minor changes to the REMS goals and timetable language to make consistent with our current standards (see Appendix A).

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21446	SUPPL-18	CP PHARMACEUTICALS CV	LYRICA (PREGABALIN) CAPSULES
NDA-22488	ORIG-1	PFIZER CHEMICAL CORP	LYRICA (PREGABALIN)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARY J DEMPSEY
12/14/2009

CLAUDIA B KARWOSKI
12/14/2009
concur